REMARKS/ARGUMENTS

The amendments to the claims are fully supported by the specification and claims as originally filed and do not constitute new matter.

Prior to the present amendment, Claims 58-66, 68-70 were pending in this application. With this amendment, Claims 58-62 have been amended to recite an "isolated native sequence polypeptide." Support for the term "native sequence" can be found in the specification at, for example, page 121, line 38 to page 122, line 11. A "native sequence PRO polypeptide" comprises a polypeptide having the same amino acid sequence as the corresponding PRO polypeptide derived from nature. Such native sequence PRO polypeptides can be isolated from nature or can be produced by recombinant or synthetic means. The term "native sequence PRO polypeptide" specifically encompasses "naturally-occurring truncated or secreted forms of the specific PRO polypeptide ... naturally occurring variant forms ... and naturally occurring allelic variants of the polypeptide."

Claims 58-63, 69 and 70 are pending after entry of the instant amendment. Applicants expressly reserve the right to pursue any canceled matter in subsequent continuation, divisional or continuation-in-part application(s).

Applicants note and appreciate the withdrawal of the earlier objections and rejections under 35 U.S.C. §112, second paragraph. The remaining rejections of Claims 58-63, 69 and 70 under 35 U.S.C. §101, §112, first paragraph, §102 and §103 are addressed below.

Priority

The Examiner asserts that Applicants are entitled to the priority of the filing date of the present application, October 15, 2001 allegedly "because the claimed invention is not supported by either a specific and substantial utility or a well established utility for the claimed polypeptides." The Examiner notes, "Applicants' response has clarified that nucleic acid of SEQ ID NO:505 and encoded protein of SEQ ID NO:506 (PRO213-1) are the same as the sequence identified as PRO1330 (clone DNA 30943) in provisional 60/100,038, which demonstrates a specific and substantial utility for the nucleic acid, as a cancer diagnostic." The Examiner further acknowledges, "Pages 61-69 of U.S. Provisional Patent Application Serial

No. 60/100,038 demonstrate that this nucleic acid is amplified in a large number of lung tumors, which was corrected for aneuploidy."

As previously stated in Applicants' response filed on October 4, 2004, Applicants rely on the gene amplification assay for patentable utility. The results of gene amplification assay in lung tumors were first disclosed in U.S. Provisional Patent Application Serial No. 60/100,038, filed on September 11, 1998 and the results of gene amplification assay in lung and colon tumors were disclosed in U.S. Provisional Patent Application Serial No. 60/131,445, filed April 28, 1999, priority to which have been claimed in this application.

Therefore, Applicants respectfully maintain the position that that the specification provides the support required to establish utility for the claimed protein, for example, in detecting over-expression or absence of expression of the PRO213-1 polypeptide for the reasons previously set forth in the Applicants' response filed on October 4, 2004. Accordingly, Applicants submit that the subject matter of the instant claims is supported by the disclosure in U.S. Provisional Patent Application Serial No. 60/100,038, filed on September 11, 1998 and in U.S. Provisional Patent Application Serial No. 60/131,445, filed April 28, 1999. Therefore, the effective filing date of this application is April 28, 1999, the filing date of U.S. Provisional Patent Application Serial No. 60/131,445.

Claim Rejections Under 35 U.S.C. §§101 and 112, First Paragraph (Enablement)

Claims 58-63 and 69-70 remain rejected under 35 U.S.C. §101 allegedly "because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility."

Claims 58-63, 69 and 70 are further rejected under 35 U.S.C. §112, first paragraph, allegedly because one skilled in the art would not know how to use the claimed invention "since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility."

For the reasons outlined below, Applicants respectfully disagree and traverse the rejections.

Utility – Legal Standard

According to 35 U.S.C. §101:

> Whoever invents or discovers any new and *useful* process, machine, manufacture, or composition of matter, or any new and *useful* improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title. (Emphasis added.)

In interpreting the utility requirement, in *Brenner v. Manson,*[1] the Supreme Court held that the quid pro quo contemplated by the U.S. Constitution between the public interest and the interest of the inventors required that a patent applicant disclose a "substantial utility" for his or her invention, *i.e.,* a utility "where specific benefit exists in currently available form."[2] The Court concluded that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion. A patent system must be related to the world of commerce rather than the realm of philosophy."[3]

Later, in *Nelson v. Bowler,*[4] the CCPA acknowledged that tests evidencing pharmacological activity of a compound may establish practical utility, even though they may not establish a specific therapeutic use. The court held that "since it is crucial to provide researchers with an incentive to disclose pharmaceutical activities in as many compounds as possible, we conclude adequate proof of any such activity constitutes a showing of practical utility."[5]

In *Cross v. Iizuka,*[6] the CAFC reaffirmed *Nelson* and added that *in vitro* results might be sufficient to support practical utility, explaining that "*in vitro* testing, in general, is relatively less complex, less time consuming, and less expensive than *in vivo* testing. Moreover, *in vitro* results

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[1] *Brenner v. Manson,* 383 U.S. 519, 148 U.S.P.Q. (BNA) 689 (1966).

[2] *Id.* at 534, 148 U.S.P.Q. (BNA) at 695.

[3] *Id.* at 536, 148 U.S.P.Q. (BNA) at 696.

[4] *Nelson v. Bowler*, 626 F. 2d 853, 206 U.S.P.Q. (BNA) 881 (C.C.P.A. 1980).

[5] *Id.* at 856, 206 U.S.P.Q. (BNA) at 883.

[6] *Cross v. Iizuka*, 753 F.2d 1047, 224 U.S.P.Q. (BNA) 739 (Fed. Cir. 1985).

with the particular pharmacological activity are generally predictive of *in vivo* test results, *i.e.*, there is a reasonable correlation there between."[7] The Court perceived "no insurmountable difficulty" in finding that, under appropriate circumstances, "*in vitro* testing, may establish a practical utility."[8]

The case law has also clearly established that applicants' statements of utility are usually sufficient, unless such statement of utility is unbelievable on its face.[9] The PTO has the initial burden that applicants' claims of usefulness are not believable on their face.[10] In general, an Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. §101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope."[11, 12]

Compliance with 35 U.S.C. §101 is a question of fact.[13] The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the totality of the evidence under consideration.[14] Thus, to overcome the presumption of truth that an assertion of utility by the applicant enjoys, the Examiner must establish that it is more likely than not that one of ordinary skill in the art would doubt the truth of the statement of utility.

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[7] *Id.* at 1050, 224 U.S.P.Q. (BNA) at 747.

[8] *Id.*

[9] *In re* Gazave, 379 F.2d 973, 154 U.S.P.Q. (BNA) 92 (C.C.P.A. 1967).

[10] *Ibid.*

[11] *In re* Langer, 503 F.2d 1380,1391, 183 U.S.P.Q. (BNA) 288, 297 (C.C.P.A. 1974).

[12] See *also In re* Jolles, 628 F.2d 1322, 206 USPQ 885 (C.C.P.A. 1980); *In re* Irons, 340 F.2d 974, 144 USPQ 351 (1965); *In re* Sichert, 566 F.2d 1154, 1159, 196 USPQ 209, 212-13 (C.C.P.A. 1977).

[13] *Raytheon v. Roper*, 724 F.2d 951, 956, 220 U.S.P.Q. (BNA) 592, 596 (Fed. Cir. 1983) *cert. denied*, 469 US 835 (1984).

[14] *In re* Oetiker, 977 F.2d 1443, 1445, 24 U.S.P.Q.2d (BNA) 1443, 1444 (Fed. Cir. 1992).

Only after the Examiner made a proper *prima facie* showing of lack of utility, does the burden of rebuttal shift to the applicant. The issue will then be decided on the totality of evidence.

The well established case law is clearly reflected in the Utility Examination Guidelines ("Utility Guidelines"),[15] which acknowledge that an invention complies with the utility requirement of 35 U.S.C. §101, if it has at least one asserted "specific, substantial, and credible utility" or a "well-established utility." Under the Utility Guidelines, a utility is "specific" when it is particular to the subject matter claimed. For example, it is generally not enough to state that a nucleic acid is useful as a diagnostic without also identifying the conditions that are to be diagnosed.

In explaining the "substantial utility" standard, M.P.E.P. §2107.01 cautions, however, that Office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. "Rather, any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient, at least with regard to defining a '"substantial" utility'."[16] Indeed, the Guidelines for Examination of Applications for Compliance With the Utility Requirement[17] gives the following instruction to patent examiners: "If the applicant has asserted that the claimed invention is useful for any particular practical purpose . . . and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility."

Proper Application of the Legal Standard

The specification provides sufficient disclosure to establish a specific, substantial and credible utility for the PRO213-1 polypeptide.

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[15] 66 Fed. Reg. 1092 (2001).

[16] M.P.E.P. §2107.01.

[17] M.P.E.P. §2107 II (B)(1).

The Examiner contends that "while the [Goddard] declaration and supporting references are convincing that the TaqMan realtime PCT method is very sensitive and can identify amplified genes, the claims are drawn to protein encoded by the PRO213-1 gene, and as discussed in the previous office action and below, it is not predictable that gene amplification results in increased mRNA expression, or that increased mRNA expression results in increased protein production." See page 4 of the instant Office Action.

Applicants respectfully submit Example 114 discloses, "Amplification is associated with overexpression of the gene product, indicating that the polypeptides are useful targets for therapeutic intervention in certain cancers such as colon, lung, breast and other cancers and diagnostic determination of the presence of those cancers." Furthermore, Table 9 teaches that PRO213-1 showed approximately 1.03-5.55 ΔCt units which corresponds to $2^{1.03}$ -$2^{5.55}$ fold amplification or 2.04 fold to 46.85-fold amplification in a number of human lung and colon tumors, which is significant. Therefore, the PRO213-1 polypeptide or a portion thereof, such as a polypeptide comprising amino acid residues 35-273, has utility as a diagnostic marker of lung or colon cancer.

Applicants respectfully disagree with the Examiner's comment that "the specification provides data showing a very small increase in DNA copy number, approximately 2-fold, in a few tumor samples for PRO213-1." See page 5 of the instant Office Action. Indeed, as stated above, PRO213-1 was found amplified 2.04 fold to 46.85-fold in at least 35 primary lung and colon tumors and tumor cell lines. (See Table 9 in the specification).

Furthermore, the previously submitted Declaration by Dr. Audrey Goddard clearly states:

> It is further my considered scientific opinion that an at least **2-fold increase** in gene copy number in a tumor tissue sample relative to a normal (*i.e.,* non-tumor) sample is significant and useful in that the detected increase in gene copy number in the tumor sample relative to the normal sample serves as a basis for using relative gene copy number as quantitated by the TaqMan PCR technique as a diagnostic marker for the presence or absence of tumor in a tissue sample of unknown pathology. Accordingly, a gene identified as being amplified at least 2-fold by the quantitative TaqMan PCR assay in a tumor sample relative to a normal sample is **useful as a marker for the diagnosis of cancer**, for monitoring cancer development and/or for measuring the efficacy of cancer therapy. (Emphasis added).

Therefore, any gene identified as being amplified at least 2-fold by the quantitative TaqMan PCR assay is considered useful as a marker for the diagnosis of cancer.

The Examiner refers to Gygi *et al.* and Pennica *et al.* and contends, "Since the instant claims are directed to PRO213-1 polypeptide, it was imperative to find evidence in the relevant scientific literature whether or not a small increase in DNA copy number would be considered by the skilled artisan to be predictive of increase mRNA and protein levels. Pennica et al. was cited as evidence showing a lack of correlation between gene (DNA) amplification and elevated mRNA levels. Gygi et al. was cited as providing evidence that protein levels cannot be accurately predicted from mRNA levels, and that variances as much as 40-fold or even 50-fold were not uncommon."

As a preliminary matter, Applicants respectfully submit that it is not a legal requirement to establish a "necessary" correlation between an increase in the copy number of the mRNA and protein expression levels that would correlate to the disease state or that it is "imperative" to find evidence that protein levels can be accurately predicted. As discussed above, the evidentiary standard to be used throughout *ex parte* examination of a patent application is a preponderance of the totality of the evidence under consideration. Accordingly, the question is not whether a necessary or even "strong" correlation between an increase in copy number and protein expression levels exists, rather if it is more likely than not that a person of ordinary skill in the pertinent art would recognize such a positive correlation. Applicants respectfully submit that when the proper evidentiary standard is applied, a correlation must be acknowledged.

Applicants respectfully submit that for the reasons previously set forth in the Applicants' response filed on October 4, 2004 that Pennica *et al.* does not show a lack of correlation between gene (DNA) amplification and elevated mRNA levels.

The Examiner alleges, "While Gygi et al. demonstrates that high levels of mRNA generally correlate with high levels of protein, it has not been demonstrated that the PRO213-1 mRNA is overexpressed at high levels. The majority of mRNAs at levels of expression other than high levels do not show a correlation with protein levels." Therefore, the Examiner concludes, "Given the small magnitude by which the DNA copy number of PRO213-1 is increased ... it is clear that one skilled in the art would not assume that a small increase in gene

copy number would correlate with significantly increased mRNA or polypeptide levels, and that it is not more likely than not that a higher level of mRNA correlates with a higher level of protein."

Applicants respectfully disagree. First of all, as mentioned above, PRO213-1 was found amplified 2.04 fold to 46.85-fold in at least 35 primary lung and colon tumors and tumor cell lines.

Further, contrary to the Examiner's reading, Gygi *et al.* clearly teach that "there was a general trend of increase protein levels resulting from increase mRNA levels." (Emphasis added. See page 1726, left column, second paragraph and Figure 5). Gygi *et al.* further states that "correlation coefficient for the whole data set (106 genes) was 0.935." In addition, Gygi *et al.* state that the correlation coefficient for genes where the message level was below 10 copies/cell was 0.356 and for most abundant proteins was 0.94. (See page 1726, second paragraph and page 1727, left column, second paragraph). Therefore, Gygi *et al.* disclose positive correlations for both lower abundant and higher abundant proteins. Applicants respectfully submit that correlation coefficient is a measure of the degree of linear relationship between two variables. A positive correlation coefficient means that as the value of one variable increases, the value of the other variable increases. Accordingly, contrary to the Examiner's position that "[t]he majority of mRNA at levels of expression other than high levels do not show a correlation with protein levels", Gygi *et al.* clearly teach that there is a general trend of increase protein levels from increase mRNA levels for all levels of mRNA expression.

In addition, Gygi *et al.* was studying steady-state yeast cells and not cancerous human cells. Gygi *et al.* further admitted that "the present study has several potential sources of error related to the methods used to determine mRNA and protein expression levels." (See page 1727, right column, second paragraph). For example, Gygi *et al.* note, "low-abundant proteins with regulatory functions such as transcription factors or protein kinases were not identified." (See page 1727, left column, first paragraph). Further, Gygi *et al.* calculated mRNA levels from frequency tables of SAGE data. For the SAGE method, the authors admit that "the error associated with a value increases with a decreasing number of transcripts per cell.... Since more than 65% of the mRNA levels included in this study were calculated to 10 copies/cell or less

(40% were less than 4 copies/cell), the error associated with these values may be quite large." (See page 1727, right column, second paragraph to page 1728, left column, first paragraph). Accordingly, Applicants respectfully submit that Gygi *et al.* did not indicate that no correlation exists between mRNA and protein levels for low abundant protein. Indeed, Gygi *et al.* showed a positive correlation for low abundant proteins indicating a general positive trend. While the correlation for low-abundant proteins may not be as strong as those shown for high abundant proteins, but as discussed above, the reason for the correlation value may be simply due the many limitations associated with using the SAGE method.

As discussed above, the law does not require the existence of a "strong" or "linear" correlation between mRNA and protein levels. Nor does the law require that protein levels be "accurately" predicted. According to the authors themselves, the Gygi data confirm that there is a general trend between protein expression and transcript levels, which meets the "more likely than not standard" and shows that a positive correlation exists between mRNA and protein. In fact, contrary to what the Examiner contends, the art indicates that, if a gene is amplified in cancer, it is more likely than not that the encoded protein will be expressed at an elevated level. As noted even in Gygi *et al.*, most genes showed a correlation between increased mRNA and translated protein. Hence, Applicants respectfully submit that based on the teachings of Gygi *et al.* and the teachings of the instant specification, one skilled in the art would more likely than not assume that the increase in gene copy number of PRO213-1 would result in an elevated level of PRO213-1 polypeptide.

The Examiner has failed to meet its initial burden of proof that Applicant's claims of utility are not substantial or credible. The arguments presented by the Examiner in combination with the Gygi paper do not provide sufficient reasons to doubt the statements by Applicants that PRO213-1 has utility. As set forth above, Gygi *et al.* supports Applicants' position that there is a positive correlation between the overexpression of mRNA and protein.

The Examiner contends that "Orntoft et al. do not appear to look at gene amplification, mRNA levels and polypeptide levels from a single gene at a time.... Orntoft et al. concentrated on regions of chromosomes with strong gains of chromosomal material containing clusters of genes (p.40). This analysis was not done for PRO213-1 in the instant specification. That is, it is

not clear whether or not PRO213-1 is in a gene cluster in a region of a chromosome that is highly amplified. Therefore, the relevance of Ornoft et al. is not clear." The Examiner further alleges, "Hyman et al. used the same CGH approach in their research. Less than half (44%) of highly amplified genes showed mRNA overexpression (abstract).... Therefore, Hyman *et al.* also do not support utility of the claimed polypeptides." The Examiner alleges that "Pollack et al. also used CGH technology concentrating on large chromosome regions showing high amplification (p. 12965). Pollack et al. did not investigate polypeptide levels. Therefore, Pollack et al. also do not support the asserted utility of the claimed invention."

In Ornoft *et al.*, 1,800 genes that yielded an increase or decrease in mRNA expression in two invasive tumors compared to the two non-invasive papillomas were then mapped to chromosomal locations. The chromosomes had already been analyzed for amplification by hybridizing tumor DNA to normal metaphase chromosomes (CGH). Ornoft *et al.* used CGH alterations as the independent variable and estimated the frequency of expression alterations of the 1,800 genes in the chromosomal areas. Ornoft *et al* found that in general (77% and 80% concordance) areas with a strong gain of chromosomal material contained a cluster of genes having increased mRNA expression (see page 40). Ornoft *et al.* state, "For both tumors TCC733 ($p<0.015$) and TCC827 ($p<0.00003$) a highly significant correlation was observed between the level of CGH ratio change (reflecting the DNA copy number) and alterations detected by the array based technology" (see page 41, column 1). Ornoft *et al.*, also studied the relation between altered mRNA and protein levels using 2D-PAGE analysis. Ornoft *et al.* state, "In general there was a highly significant correlation ($p<0.005$) between mRNA and protein alterations.... 26 well focused proteins whose genes had a known chromosomal location were detected in TCCs 733 and 335, and of these 19 correlated ($p<0.005$) with the mRNA changes detected using the arrays." (See page 42, column 2 to page 34, column 2). Accordingly, Ornoft *et al.* clearly support Applicants position that proteins expressed by genes that are amplified in tumors are useful as cancer markers.

The Examiner indicates that Applicants have not indicated whether PRO213-1 is in a gene cluster region of a chromosome. (See page 6 of the instant Office Action). Applicants fail to see how this is relevant to the analysis. Ornoft *et al.* did not limit their findings to only those

regions of amplified gene clusters. Further, as discussed below, Hyman *et al.* and Pollack *et al.* did gene-by-gene analysis across all chromosomes.

The Examiner has mischaracterized the methods used by Hyman *et al.* and Pollack *et al* in their analysis. These papers did not use traditional CGH analysis to identify amplified genes. In Hyman *et al.*, 13,824 cDNA clones were placed on glass slides in a microarray and genomic DNA from breast cancer cell lines and normal human WBCs were hybridized to the cDNA sequences. For expression analysis, RNA from tumor cell lines were hybridized on the same microarrays. The 13,824 arrayed cDNA clones were analyzed for gene expression and gene copy number in 14 breast cancer cell lines. Hyman *et al.* state, "The results illustrate a considerable influence of copy number on gene expression patterns." For example, Hyman *et al.* teach that "[u]p to 44% of the highly amplified transcripts (CGH ratio, >2.5) were overexpressed (*i.e.*, belonged to the global upper 7% of expression ratios) compared with only 6% for genes with normal copy number." (See page 6242, column 1). Further, Hyman *et al.* state that "[t]he cDNA/CGH microarray technique enables the direct correlation of copy number and expression data on a gene-by-gene basis throughout the genome." (See page 6242, column 2). Therefore, the analysis performed by Hyman *et al.* was on a gene-by gene basis, and clearly shows that "it is more likely than not" that a gene which is amplified in tumor cells will have increased gene expression.

In Pollack *et al.*, DNA copy number alteration across 6,691 mapped human genes in 44 predominantly advanced primary breast tumors and 10 breast cancer cell lines was profiled. Pollack *et al.* further state, "Parallel microarray measurements of mRNA levels reveal the remarkable degree to which variation in gene copy number contributes to variation in gene expression in tumor cells." (See Abstract). "Genome-wide, of 117 high-level DNA amplifications (fluorescence ratios >4, and representing 91 different genes), 62% (representing 54 different genes; ...) are found associated with at least moderately elevated mRNA levels (mean-centered fluorescence ratios >2), and 42% (representing 36 different genes) are found associated with comparably highly elevated mRNA levels (mean-centered fluorescence ratios >4)." (See page 12966, column 1). Therefore, the analysis performed by Pollack *et al.* was also

on a gene-by gene basis, and clearly shows that "it is more likely than not" that a gene which is amplified in tumor cells will have increased gene expression.

The Examiner also alleges that papers by Orntoft *et al.*, Hyman *et al.* and Pollack *et al.* "state that the research was relevant to the development of potential cancer therapeutics, but also clearly imply that much further research was needed before such therapeutics were in readily available form. Accordingly, the specification's assertion that the claimed PRO213-1 proteins have utility in the fields of cancer diagnostics and cancer therapeutics are not substantial."

Applicants respectfully disagree.

As stated above, in explaining the "substantial utility" standard, M.P.E.P. §2107.01 cautions that Office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. "Rather, any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient, at least with regard to defining a '"substantial" utility'."[18] Indeed, the Guidelines for Examination of Applications for Compliance With the Utility Requirement[19] states, "If the applicant has asserted that the claimed invention is useful for any particular practical purpose . . . and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility.

Applicants have clearly shown that based upon the gene amplification results that there is a clear correlation between the amplification and overexpression of the PRO213-1 gene and lung and colon tumors. Accordingly, Applicants respectfully submit that Applicants' assertion that the claimed PRO213-1 proteins have utility in the field of cancer diagnostics is substantial.

With regard to the correlation between mRNA expression and protein levels, Applicants previously submitted a Declaration by Dr. Polakis, principal investigator of the Tumor Antigen Project of Genentech, Inc., the assignee of the present application, to show that mRNA

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[18] M.P.E.P. §2107.01.

[19] M.P.E.P. §2107 II (B)(1).

expression correlates well with protein levels, in general. As Dr. Polakis explains, the primary focus of the microarray project was to identify tumor cell markers useful as targets for both the diagnosis and treatment of cancer in humans. The scientists working on the project extensively rely on results of microarray experiments in their effort to identify such markers. As Dr. Polakis explains, using microarray analysis, Genentech scientists have identified approximately 200 gene transcripts (mRNAs) that are present in human tumor cells at significantly higher levels than in corresponding normal human cells. To date, they have generated antibodies that bind to about 30 of the tumor antigen proteins expressed from these differentially expressed gene transcripts and have used these antibodies to quantitatively determine the level of production of these tumor antigen proteins in both human cancer cells and corresponding normal cells. Having compared the levels of mRNA and protein in both the tumor and normal cells analyzed, they found a very good correlation between mRNA and corresponding protein levels. Specifically, in approximately 80% of their observations they have found that increases in the level of a particular mRNA correlates with changes in the level of protein expressed from that mRNA. While the proper legal standard is to show that the existence of correlation between mRNA and polypeptide levels is more likely than not, the showing of approximately 80% correlation for the molecules tested in the Polakis Declaration greatly exceed this legal standard. Based on these experimental data and his vast scientific experience of more than 20 years, Dr. Polakis states that, for human genes, increased mRNA levels typically correlate with an increase in abundance of the encoded protein. He further confirms that "it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded protein."

The Examiner contends that Dr. Polakis Declaration is insufficient to overcome the rejection of claims 58-63, 69 and 70 since it is limited to a discussion of data regarding the correlation of mRNA levels and polypeptide levels and not gene amplification levels. The examiner further alleges that only Dr. Polakis' conclusions are provided in the Declaration. Thus, the Examiner asserts that there is no evidentiary support to Dr. Polakis statement that it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded polypeptide.

Applicants submit that Dr. Polakis' Declaration is presented to support the position that there is a correlation between mRNA levels and polypeptide levels. Regarding the Examiner's rejection of the Polakis Declaration "for not being supported by evidence of record," Applicants emphasize that the opinions expressed in the Polakis Declaration, including the quoted statement, are all based on factual findings. Thus, Dr. Polakis explains that in the course of their research using microarray analysis, he and his co-workers identified approximately 200 gene transcripts that are present in human tumor cells at significantly higher levels than in corresponding normal human cells. Subsequently, antibodies binding to about 30 of these tumor antigens were prepared, and mRNA and protein levels were compared. In approximately 80% of the cases, the researchers found that increases in the level of a particular mRNA correlated with changes in the level of protein expressed from that mRNA when human tumor cells are compared with their corresponding normal cells. Dr. Polakis' statement that "an increased level of mRNA in a tumor cell relative to a normal cell typically correlates to a similar increase in abundance of the encoded protein in the tumor cell relative to the normal cell" is based on factual, experimental findings, clearly set forth in the Declaration. Accordingly, the Declaration is not merely conclusive, and the fact-based conclusions of Dr. Polakis would be considered reasonable and accurate by one skilled in the art.

The case law has clearly established that in considering affidavit evidence, the Examiner must consider all of the evidence of record anew.[20] "After evidence or argument is submitted by the applicant in response, patentability is determined on the totality of the record, by a preponderance of the evidence with due consideration to persuasiveness of argument."[21] Furthermore, the Federal Court of Appeals held in *In re* Alton, "We are aware of no reason why opinion evidence relating to a fact issue should not be considered by an examiner."[22] Applicants

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[20] *In re* Rinehart, *531* F.2d 1084, 189 USPQ 143 (C.C.P.A. 1976); *In re* Piasecki, 745 F 2d. 1015, 226 USPQ 881 (Fed. Cir. 1985).

[21] *In re* Alton, 37 USPQ2d 1578, 1584 (Fed. Cir 1996) (quoting *In re* Oetiker, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992)).

[22] *In re* Alton, *supra.*

also respectfully draw the Examiner's attention to the Utility Examination Guidelines[23] which states, "Office personnel must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned; it is improper to disregard the opinion solely because of a disagreement over the significance or meaning of the facts offered." The statement in question from an expert in the field (the Polakis Declaration) states that "it is my considered scientific opinion that for human genes, an increased level of mRNA in a tumor cell relative to a normal cell typically correlates to a similar increase in abundance of the encoded protein in the tumor cell relative to the normal cell." Therefore, barring evidence to the contrary regarding the above statement in the Polakis Declaration, this rejection is improper under both the case law and the Utility guidelines.

Taken together, although there are some examples in the scientific art that do not fit within the central dogma of molecular biology that there is a correlation between polypeptide and mRNA levels, these instances are exceptions rather than the rule. In the majority of amplified genes, the teachings in the art, as exemplified by Orntoft *et al.,* Hyman *et al.,* Pollack *et al.,* and the Polakis Declaration, overwhelmingly show that gene amplification influences gene expression at the mRNA and protein levels. Therefore, one of skill in the art would reasonably expect in this instance, based on the amplification data for the PRO213-1 gene, that the PRO213-1 polypeptide is concomitantly overexpressed. Thus, Applicants submit that the PRO213-1 polypeptides and antibodies have utility in the diagnosis of cancer and based on such a utility, one of skill in the art would know exactly how to use the antibody for diagnosis of cancer.

The Examiner cites Hu *et al.* for support that genes displaying a 5-fold change or less in mRNA expression in tumors compared to normal showed no evidence of a correlation between altered gene expression and a known role in the disease. However, among genes with a 10-fold or more change in expression level, there was a strong and significant correlation between expression level and a published role in the disease.

Applicants submit that in order to overcome the presumption of truth that an assertion of utility by the applicant enjoys, the Examiner must establish that it is more likely than not that one

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[23] Part IIB, 66 Fed. Reg. 1098 (2001).

of ordinary skill in the art would doubt the truth of the statement of utility. Accordingly, contrary to the Examiner's assertion, Applicants respectfully submit that Hu *et al.* does not conclusively show that it is more likely than not that the gene amplification does not result in increased expression at the mRNA and polypeptide levels.

First, the title of Hu *et al.* is "Analysis of Genomic and Proteomic Data Using Advanced Literature Mining." As the title clearly suggests, the conclusion suggested by Hu *et al.* is merely based a statistical analysis of the information disclosed in published literatures. As Hu *et al.* states, "We have utilized a computational approach to literature mining to produce a comprehensive set of gene-disease relationships." In particular, Hu *et al.* relied on MedGene Database and the Medical Subject Heading (MeSH) files to analyze the gene-disease relationship. More specifically, Hu *et al.* "compared the MedGene breast cancer gene list to a gene expression data set generated from a micro-array analysis comparing breast cancer and normal breast tissue samples." (See page 408, right column).

Therefore, Applicants submit that the reference by Hu *et al.* only studies the statistical analysis of micro-array data and not the gene amplification data. Hence, their findings would not be directly applicable to the gene amplification data. In addition, the Hu *et al.* reference does not show a lack of correlation between microarray data and the biological significance of cancer genes.

Further, the analysis by Hu *et al.* has certain statistical flaws. According to Hu *et al.*, "*different* statistical methods" were applied to "*estimate* the strength of gene-disease relationships and evaluated the results." (See page 406, left column, emphasis added). Using these different statistical methods, Hu *et al.* "[a]ssessed the relative strengths of gene-disease relationships based on the frequency of both co-citation and single citation." (See page 411, left column). It is well known in the art that various statistical methods allow different variables to be manipulated to affect the outcome. For example, the authors admit, "Initial attempts to search the literature using" the list of genes, gene names, gene symbols, and frequently used synonyms, generated by the authors "revealed several sources of false positives and false negatives." (See page 406, right column). The authors further admit that the false positives caused by "duplicative and unrelated meanings for the term" were "difficult to manage." Therefore, in

order to minimize such false positives, Hu *et al.* disclose that these terms "had to be eliminated entirely, thereby reducing the false positive rate but unavoidably under-representing some genes." *Id.* (emphasis added). Hence, Applicants respectfully submit that in order to minimize the false positives and negatives in their analysis, Hu *et al.* manipulated various aspects of the input data.

Applicants further submit that the statistical analysis by Hu *et al.* is not a reliable standard because the frequency of citation only reflects the current research interest of a molecule but not the true biological function of the molecule. Indeed, the authors acknowledge that "[r]elationship established by frequency of co-citation do not necessarily represent a true biological link." (See page 411, right column). It often happens in the scientific study that important molecules were overlooked by the scientific society for many years until the discovery of their true function. Therefore, Applicants submit that Hu *et al.* drew their conclusion based on a very unreliable standard and their research does not provide any meaningful information regarding the correlation between the microarray data and the biological significance.

Even assuming that Hu *et al.* provide evidence to support a true relationship, the conclusion in Hu *et al.* only applies to a specific type of breast tumor (estrogen receptor (ER)-positive breast tumor) and can not be generalized as a principle governing microarray study of breast cancer in general, let alone the various other types of cancer genes in general. In fact, even Hu *et al.* admit that "[i]t is likely that this threshold will change depending on the disease as well as the experiment. Interestingly, the observed correlation was only found among ER-positive (breast) tumors not ER-negative tumors." (See page 412, left column). Therefore, based on these findings, the authors add, "This may reflect a bias in the literature to study the more prevalent type of tumor in the population. Furthermore, this emphasizes that caution must be taken when interpreting experiments that may contain subpopulations that behave very differently." *Id.* (emphasis added).

Accordingly, Applicants respectfully submit that the Examiner has not shown that a lack of correlation between microarray data and the biological significance of cancer genes.

The Examiner contends that the Ashkenazi Declaration is insufficient to overcome the rejection of Claims 58-63, 69 and 70. In particular, the Examiner alleges, "If a specific gene

product was known to be involved in cancer and if there were known compounds that could be used to target the gene product, this would be an acceptable utility. However, the gene product of the instant invention has not been demonstrated to be involved in cancer." The Examiner further alleges, "The Hanna reference is not applicable to the instant fact situation, as it deals with a known tumor associated gene, and not with a prospective analysis of the type found in this specification."

Applicants respectfully disagree. Applicants have clearly shown that the gene encoding PRO213-1 polypeptide is amplified in at least 35 primary lung and colon tumors and lung and colon cell lines. Therefore, PRO213-1 gene, similar to HER-2/neu gene disclosed in Hanna *et al.*, is a tumor associated gene. Furthermore, as discussed above, in the majority of amplified genes, the teachings in the art overwhelmingly show that gene amplification influences gene expression at the mRNA and protein levels. Therefore, one of skill in the art would reasonably expect in this instance, based on the amplification data for the PRO213-1 gene, that the PRO213-1 polypeptide is concomitantly overexpressed. However, even if gene amplification does not result in overexpression of the gene product (*i.e.,* the protein) an analysis of the expression of the protein is useful in determining the course of treatment. As indicated by Dr. Ashkenazi in his Declaration, Applicants submit that simultaneous testing of gene amplification and gene product over-expression enables more accurate tumor classification, even if the gene product (the protein) is not over expressed.

In conclusion, Applicant submits that the present rejection is based on the application of an incorrect, elevated legal standard, on misconstruction of the references and erroneous conclusions drawn therefrom. The issue of patentable utility should be assessed on the totality of evidence, using the preponderance evidentiary standard. It is submitted that on the totality of evidence Applicants clearly established that the claimed invention has a substantial, specific and credible utility. Further, based on this utility and the disclosure in the specification, one skilled in the art at the time the application was filed would know how to use the claimed polypeptides. Accordingly, Applicants request the Examiner to reconsider and withdraw the rejection of Claims 58-63. 69 and 70 under 35 U.S.C. §§101 and 112.

Claim Rejection Under 35 U.S.C. §112, First Paragraph (Written Description)

Claims 58-62, 69 and 70 remain rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s) at the time the application was filed, had possession of the claimed invention.

Applicants respectfully submit that as amended, the claims are drawn to native sequence polypeptides at least 80-99% identical to the amino acid sequence of amino acid residues 35-273 of SEQ ID NO:506. The Examiner states that "the only factors present in the claim are functional, in that the protein of SEQ ID NO:506 is encoded by a nucleic acid that is amplified in lung cancer." The Examiner further alleges, "It is clear that while there *could* be additional polypeptides that meet the limitations of the claims, that conception of such polypeptides has not occurred, and cannot occur until their actual isolation, as it is not predictable what additional mutations in SEQ ID NO:506 would occur in nature and further be associated with lung cancer." Accordingly, the Examiner concludes that "polypeptides comprising the sequence set forth in SEQ ID NO:506, but not the full breadth of the claims meet the written description provision of 35 U.S.C. §112 first paragraph."

Applicants respectfully disagree and traverse the rejection.

The Legal Test for Written Description

The well-established test for sufficiency of support under the written description requirement of 35 U.S.C. §112, first paragraph, is "whether the disclosure of the application as originally filed reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter, rather than the presence or absence of literal support in the specification for the claim language."[24, 25] The adequacy of written description support is a factual issue and is to be determined on a case-by-case basis.[26] The factual determination in a

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[24] *In re* Kaslow, 707 F.2d 1366, 1374, 212 USPQ 1089, 1096 (Fed. Cir. 1983).

[25] See *also Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at 1563, 19 USPQ2d at 1116 (Fed. Cir. 1991)

[26] *See e.g., Vas-Cath*, 935 F.2d at 1563; 19 USPQ2d at 1116.

written description analysis depends on the nature of the invention and the amount of knowledge imparted to those skilled in the art by the disclosure.[27, 28]

In *Environmental Designs, Ltd. v. Union Oil Co.*,[29] the Federal Circuit held, "Factors that may be considered in determining level of ordinary skill in the art include: (1) the educational level of the inventor; (2) type of problems encountered in the art; (3) prior art solutions to those problems; (4) rapidity with which innovations are made; (5) sophistication of the technology; and (6) educational level of active workers in the field." (Emphasis added).[30] Further, The "hypothetical 'person having ordinary skill in the art' to which the claimed subject matter pertains would, of necessity have the capability of understanding the scientific and engineering principles applicable to the pertinent art."[31, 32].

The Disclosure Provides Sufficient Written Description for the Claimed Invention

Applicants have amended Claims 58-62 to recite an isolated native sequence polypeptide. Applicants respectfully submit that the instant specification evidences the actual reduction to practice of the amino acid sequence of amino acid residues 35-273 of SEQ ID NO:506. As stated above, the Examiner has acknowledged that polypeptides comprising the sequence set forth in SEQ ID NO:506 meet the written description provision of 35 U.S.C. §112, first paragraph. Thus, the genus of native sequence polypeptides with at least 80% sequence identity to SEQ ID NO:506, which possess the functional property of having a nucleic acid which is

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[27] *Union Oil v. Atlantic Richfield Co.*, 208 F.2d 989, 996 (Fed. Cir. 2000).

[28] *See also* M.P.E.P. §2163 II(A).

[29] 713 F.2d 693, 696, 218 USPQ 865, 868 (Fed. Cir. 1983), *cert. denied*, 464 U.S. 1043 (1984)

[30] *See also* M.P.E.P. §2141.03.

[31] *Ex parte Hiyamizu*, 10 USPQ2d 1393, 1394 (Bd. Pat. App. & Inter. 1988) (emphasis added).

[32] S*ee also* M.P.E..P. §2141.03.

amplified in colon or lung tumors would meet the requirement of 35 U.S.C. §112, first paragraph, as providing adequate written description.

Applicants have provided native PRO sequence SEQ ID NO:506. The present application also describes methods for identifying genes which are amplified in colon or lung cancer.

Example 114 of the present application provides step-by-step guidelines and protocols for the gene amplification assay. By following the disclosure in the specification, one skilled in the art can easily test whether a gene encoding a native variant PRO213-1 protein is amplified in colon or lung tumors. The specification further describes methods for the determination of percent identity between two amino acid sequences. (See pages 122, line 34 to page 125, line 37). In fact, the specification teaches specific parameters to be associated with the term "percent identity" as applied to the present invention. Accordingly, one of skill in the art could identify whether the variant PRO213-1 native sequence falls within the parameters of the claimed invention. Once such an amino acid sequence was identified, the specifications sets forth methods for making the amino acid sequences (see page 180, line 9 to page 184, line 35) and methods of preparing the PRO polypeptides (see page 185, line 36 and onward).

Therefore, Applicants respectfully submit that one of skill in the art could readily test a nucleic acid sequence which encodes the variant polypeptide to determine whether it is amplified by the methods set forth in Example 114.

Accordingly, the specification provides adequate written description for native sequence polypeptides having at least 80% identity to SEQ ID NO:506 wherein the nucleic acid encoding the polypeptide is amplified in colon or lung tumors. For the above reasons, Applicants respectfully request that the rejection be withdrawn and the claims be allowed.

Claim Rejections Under 35 U.S.C. §102

Claims 58-63 and 69 remain rejected and Claims 78-84 are rejected under 35 U.S.C. §102(e) as being anticipated by Holtzman *et al.* (U.S. Published Patent Application 20020028508), with an effective priority date of April 23, 1998. In particular, the Examiner alleges that Holtzman *et al.* disclose a protein that is 100% identical to the protein of SEQ ID NO:506.

Claims 58-62, 69 and 70 stand rejected under 35 U.S.C. §102(e) as allegedly being anticipated by Sheppard *et al.* (U.S. Published Patent Application 20030166907) ("Sheppard"), with an effective priority date of June 18, 1997. In particular, the Examiner alleges that Sheppard *et al.* disclose a protein that is 99% identical to the protein of SEQ ID NO: 506.

Claims 58-62 were amended to recite, "An isolated native sequence polypeptide comprising a sequence having at least 80% amino acid sequence identity to the amino acid sequence of amino acid residues 35-273 of SEQ ID NO:506."

In addition, Applicants respectfully submit Declarations under 37 C.F.R. §1.131 by Dr. Goddard, Dr. Godowski, Dr. Gurney, Ms. Roy and Dr. Wood, that establish that Applicants had sequenced, cloned and homology human growth arrest-specific 6 (gas6) protein identified for the claimed polypeptides before June 18, 1997, which is earliest than the effective priority date of Holtzman *et al.* and Sheppard *et al.* The consideration of the Declarations is respectfully requested.

Applicants need to disclose only what is disclosed in the cited reference to support their priority claim

Applicants respectfully submit that in order to overcome the 35 U.S.C. §102(e) rejection over Holtzman *et al.* and and Sheppard *et al* and support the priority claim, the Declarations by Dr. Goddard, Dr. Godowski, Dr. Gurney, Ms. Roy and Dr. Wood ("Declarations") simply need to provide a disclosure commensurate in scope with the disclosure in the prior art document by Holtzman *et al.* and and Sheppard *et al.*

In order to remove a reference as a prior art, "[i]t is sufficient if [the affidavit under Patent Office Rule 131] shows that as much of the claimed invention as is taught in the reference has been reduced to practice by the [patentee] prior to the date of the reference." *In re* Stempel,

241 F.2d 755, 757 (1957). In *In re* Stempel, the patent applicant (Stempel) had claims directed to both: (i) a particular genus of chemical compounds (the "generic" claim), and (ii) a single species of chemical compound that was encompassed within that genus (the "species" claim). In support of a rejection under 35 U.S.C. §102, the examiner cited against the application a prior art reference that disclosed the exact chemical compound recited in the "species" claim. In response to the rejection, the patent applicant filed a declaration under 37 C.F.R. §1.131 demonstrating that he had made that specific chemical compound prior to the effective date of the cited prior art reference. The Court found the applicant's 37 C.F.R. § 1.131 declaration effective for swearing behind the cited reference for purposes of both the "species" claim and the "genus" claim. Specifically, the Court stated in support of its decision that "all the applicant can be required to show is priority with respect to so much of the claimed invention as the reference happens to show. When he has done that he has disposed of the reference." *Id.* at 759.

Furthermore, the Examiner is respectfully directed to *In re* Moore, 170 USPQ 260 (CCPA 1971), where the holding in *In re* Stempel was affirmed. In *In re* Moore, the patent applicant claimed a particular chemical compound in his patent application and the examiner cited against the applicant a prior art reference under 35 U.S.C. §102 rejection which disclosed the compound but did not disclose any specific utility for the compound. The patent applicant filed a declaration under 37 C.F.R. §1.131 demonstrating that he had made the claimed compound before the effective date of the cited prior art reference, even though he had not yet established a utility for that compound. On appeal, the Court indicated that the 131 declaration filed by the patent applicant was sufficient to remove the cited reference. The Court relied on the established "Stempel Doctrine" to support its decision, stating:

> An applicant need **not** be required to show [in a declaration under 37 C.F.R. §1.131] any more acts with regard to the subject matter claimed that can be carried out by one of ordinary skill in the pertinent art following the description contained in the reference ... the determination of a practical utility when one is not obvious need **not** have been accomplished prior to the date of a reference unless the reference also teaches how to use the compound it describes.

In re Moore, 170 USPQ at 267 (emphasis added).

Thus, *In re* Moore confirmed the holding in *In re* Stempel which states that in order to effectively remove a cited reference with a declaration under 37 C.F.R. §1.131, an applicant need only show that portion of his or her claimed invention that appears in the cited reference.

Accordingly, Applicants respectfully submit that the Declarations simply need to show possession of the polypeptide sequence and its encoding polynucleotide sequence and the homology of the polypeptide to other families whose functions are known in the art as disclosed in Holtzman *et al* and Sheppard *et al.* in order to overcome the 35 U.S.C. §102 rejection over these two references.

As shown in the Declarations, Applicants respectfully submit that the PRO213 polypeptide comprising amino acid residues 35-273 of SEQ ID NO:506 in the present application was sequenced and cloned in the United States prior to June 18, 1997, the effective priority date of Sheppard *et al.* The polypeptide also shown to have homology to human gas6 protein before the priority date of April 23, 1998.

As indicated in the Declarations and the brief description of Figure 1 of the present specification, the PRO213 polypeptide is encoded by DNA30943-1163.

Furthermore, as stated in the Declarations, the GSeqEdit database and GenenGenes database store cloning, sequencing and functional information for each PRO polypeptide and its encoding nucleic acid sequences according to its DNA number. Copies of the pages from the GSeqEdit database report and GenenGenes database report (with the dates redacted) showing the cloning, sequencing and homology information for the PRO213 and 213-1 polypeptide sequences and their encoding nucleic acid sequences are attached to the Declarations as Exhibit A. PRO213 comprises the amino acid sequence of the polypeptide having an amino acid sequence of residues 35-273 of SEQ ID NO: 506.

The GSeqEdit report shows the full length nucleic acid sequence for DNA30943-1-1163 (PRO213-1) and the full length polypeptide sequence encoded by DNA30943-1163. As evidenced from the report and stated in the Declarations, the amino acid sequence comprising residues 35-273 of SEQ ID NO: 506 as shown in Exhibit A was obtained prior to June 18, 1997, the priority date of Sheppard *et al.*.

In addition, as stated in the Declarations, the sequence of amino acid residues 57 to 295 of PRO213 polypeptide shown in Figure 2 and amino acids 35 to 273 shown in GSeqEdit report are identical to that of amino acids 35 to 273 of SEQ ID NO:506 disclosed in the above-identified application. Further, the Declaration notes that the portion of the PRO213 polypeptide, which is identical to the portion of the PRO213-1 polypeptide is significantly homologous with the human growth arrest-specific 6 (gas6) protein. The homology of PRO213 to human gas6 was obtained prior to June 18, 1997.

Accordingly, the Declarations along with attached Exhibit A clearly show that Applicants were in possession of DNA30943-1163, the polypeptide encoded by DNA30943-1163, and the homology functional information prior to June 18, 1997, the priority date of Sheppard *et al.* Therefore, the Declarations further establish that the claimed polypeptide sequence, residues 35-273 of SEQ ID NO:506, was sequenced and cloned, and its homology determined prior to June 18, 1997 and April 23, 1998.

Consequently, based on the holdings of *In re* Stempel and *In re* Moore, Applicants respectfully submit that Holtzman *et al.* and Sheppard *et al.* is not prior art under 102(e) since their effective priority date is after the date the instant invention was conceived and reduced to practice in the United States.

Claim Rejections Under 35 U.S.C. §103(a)

Claims 70 remain rejected under 35 U.S.C. §103(a) as being unpatentable over Holtzman *et al* in view of Hopp *et al.* Applicants respectfully disagree with this rejection.

For the reasons previously set forth in the Applicants' response filed on October 4, 2004 and above, Applicants respectfully submit that Holtzman *et al.* is not prior art. Accordingly, since the primary reference, Holtzman *et al.* is not prior art, this rejection falls and Applicants submit that Claim 70 is not obvious over Holtzman *et al.* in view of Hopp *et al.* Hence, Applicants request that the rejection of Claims 70 under 35 U.S.C. § 103(a) as being as being unpatentable over Holtzman *et al.* in view of Hopp *et al.* be withdrawn.

CONCLUSION

In conclusion, the present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited. Should there be any further issues outstanding, the Examiner is invited to contact the undersigned attorney at the telephone number shown below.

Although no fees are due, the Commissioner is hereby authorized to charge any fees, including any fees for extension of time, or credit overpayment to Deposit Account No. **08-1641**, referencing Attorney's Docket No. **39780-2630 P1C4**. Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

Date: May 23, 2005

By: _____
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